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Biokinetics
42

Kinetics of lead in blood after the end of occupational exposure

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SCHÜTZ A, SKERFVING S, RANSTAM J, CHRISTOFFERSSON J-O. Kinetics of lead in blood after the end of occupational exposure. *Scand J Work Environ Health* 13 (1987) 221—231. The sum of two exponential functions was fitted to the decay of blood lead (PbB) level after the end of lead exposure. For two subjects who had not formerly been occupationally exposed to lead but who had been exposed to a single short heavy dose, the fast compartment (probably soft tissues) had a biological half-time of ... and 44 d, respectively. For 20 lead workers after the end of occupational exposure, the corresponding median was 29 (range 7—63) d. For 21 ex-lead workers, the median biological half-time of the slow compartment was 5.6 (range 2.3—27) years. There was significant interindividual variation in both the fast and the slow half-time. This finding probably means a considerable variation in risk at a certain exposure level. In the lead workers, the PbB fraction corresponding to the slow compartment had a median as high as 1.8 (range 0.7—2.7) μmol/l, which constituted more than half of the total PbB. This fraction was associated with exposure history, and with the lead level in the skeleton, the latter determined in vivo by an X-ray fluorescence method. The data thus indicate a rather rapid turnover of the skeletal lead pool, a phenomenon which may affect the PbB level considerably.

Key terms: half-time, metabolic model, two-compartment model.

...exposure is common in industry. The blood lead ...d) level is the main parameter used for the bio... monitoring of lead exposure (74). However, ...ledge on the kinetics of PbB is incomplete, as it ...arding the metabolism of lead in the other tis... the body (74), which is a phenomenon that PbB ... mirror.

...the present article we report a study of the decay ...rn of lead in the blood of lead-exposed subjects ... the end of exposure. This decay pattern could ...terpreted by a metabolic model.

...bjects and methods

...xperts and sampling

...e first group to be studied was 23 male ex-lead work... (table 1). Their mean age was 55 years and their ...an exposure time was 23 years. The PbB was usually ...rmined at the end of exposure and then at varying ...ervals. For ten subjects PbB was determined once, ...more often, a year. For one worker (number 101), ...information was available concerning the first year ...r the end of exposure. For 12 subjects (numbers ...—115), several determinations were made during ...e first year, then at year seven, and then again from ...r nine on about twice a year. For one subject (number 102) there was a lack of data between 3.5 and 9.6 years after the end of exposure.

In addition 17 male lead workers temporarily removed from exposure were investigated (table 2). Their mean age was 49 years, and their mean exposure time was 11 years. The reason for removal from exposure was high PbB levels (generally about 3.0 μmol/l or more). Twelve of the workers were transferred from a smeltery to a nearby plant, the work in which did not involve lead exposure. The PbB level was generally determined when the workers left the smeltery and then once a week for three weeks; later PbB measurements were made once every two to four weeks.

Furthermore, two male volunteers, who had been unexposed occupationally, but who had been exposed to a single short heavy lead dose, were included (table 2). Details on these two subjects have been published elsewhere (56).

Spot determinations of "background" PbB levels were made for 47 healthy workers not occupationally exposed to lead. They lived in the same county as the exposed subjects and were all blue-collar workers. Their average PbB level was 0.3 μmol/l. In this connection, it may be mentioned that, for 15 workers in a glue production plant located close to the nonlead resort of the temporarily removed smeltery workers, the average PbB level was 0.5 (range 0.3—0.7) μmol/l.

Medical examinations

For most of the subjects, an occupational and medical history, including alcohol habits, was obtained. Venous blood samples were analyzed for lead (see the section Blood Lead Determinations), hemoglobin, sedimentation rate; red and white cell counts; calcium,

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phosphate, and creatinine concentrations; and alkaline phosphatase and gamma glutamyl transferase activities in serum. A urine sample was analyzed for albumin and glucose.

Among the ex-lead workers, detailed medical information was lacking for four. Among the 19 remaining, 12 had earlier been removed (at least once) temporarily from lead exposure because of a high PbB level and/or a high delta-aminolevulinic acid level in the urine. One subject was clinically diagnosed as lead poisoned (upper abdominal pain, constipation, neuropathy, and slight anemia) at the time when his exposure ended. No one else had been treated in a hospital because of lead poisoning. One worker had a clinically silent chronic lymphatic leukemia, and one had a type 2 diabetes treated with diet only. Three persons had slight increases in their serum creatinine levels, and two others showed slight albuminuria. Three subjects had somewhat increased gamma glutamyl transferase activities, in their serum, two of whom were known to abuse alcohol.

Among the 17 temporarily removed lead workers, detailed medical information was available for 14. Among these 14, seven had earlier been removed because of a high PbB level and/or a high delta-aminolevulinic acid level in their urine. None had been treated with drugs because of lead poisoning. Three subjects had slightly increased gamma glutamyl transferase activities in their serum, one of whom also had an increased alkaline phosphatase activity in his serum. One person had an isolated marginal increase in alkaline phosphatase activity in his serum.

The two subjects without previous occupational lead exposure were both in excellent health.

Blood lead determinations

Blood was obtained from the cubital vein. During the first years of the study, acid-washed heparinized sampling tubes were prepared at our laboratory. Later on, evacuated, metal-free Vacutainer® tubes were used.

Almost all of the PbB determinations were made in the same laboratory and by the same method. The samples were wet-ashed, and lead was complexed with dithizone, extracted, and determined by flame atomic absorption spectrometry (AAS) (55, 56). The detection limit was 0.05 μmol/l (10 μg/l).

Each analytical series contained six samples, two blanks containing reagents only, and four "normal" blood samples (two of them with standard lead addition). All the samples were analyzed twice. The coefficient of variation calculated from duplicate analyses of 25 samples containing 0.5 μmol/l or less was 6.6 % of the mean, for 57 samples containing 0.5—1 μmol/l it was 3.9 %, for 58 samples containing 1—2 μmol/l it was 2.5 %, and for 60 samples containing 2—3.5 μmol/l it was 2.0 %.

The accuracy was tested twice each year in a Nordic interlaboratory calibration program with 6—19 (mean 12) accepted laboratories participating on each occasion. The regression function of our results (Y, μmol/l) on the average result of the other laboratories (X) was $Y = 1.008X - 0.052$. Our results for the 115 samples (range 0.2—5.6 μmol/l) averaged 96.3 % of the mean (range 80—112 %; 62 % within 95—105 %) of the other laboratories. Furthermore, we participated in the Swedish External Quality Assessment Scheme during the last part of the study. In the 29 samples analyzed, our results by single analysis averaged 99 % of the mean (range 0.2—5.6 μmol/l) (range 90—115 %; 72 % within 95—105 %) of the about 90 participating laboratories. Neither quality control series displayed any time trend.

During the first year of observation of subjects 104—115, the first three years of subject 102, and the six first years of subject 116, PbB was determined by a colorimetric method after extraction with dithizone in chloroform. The detection limit was about 0.6 μmol/l. The results obtained by the colorimetric method averaged 105 (SD 6) % in the concentration range 0.3—1.9 μmol/l and 100 (SD 5) % in the range 2.0—5.4 μmol/l of results obtained with the flame AAS method.

From subject 116, for the following four years determinations were made by flame AAS after precipitation of proteins with trichloroacetic acid (22). The detection limit was 0.2 μmol/l, and the method error about 10 %.

Mathematical analysis

Three models corresponding to the sum of one, two, and three exponentials were considered for the PbB decay curves of each individual worker. A fixed "background" value of 0.3 μmol/l was used for all the subjects and each model. The nonlinear regression procedure in the statistical package BMDP (21) was used. This program produces estimates of the parameters which minimize the unweighted residual sum of squares using a modified Gauss-Newton algorithm. Minimum and maximum values can be specified for each parameter. Thus two parameters and their asymptotic standard deviation were estimated: an elimination rate [transformed and quoted as half-time T½(1), T½(2), and T½(3)] and the concentration corresponding to each compartment [Y(1), Y(2), and Y(3)]. Confidence intervals were estimated on the assumption of asymptotic normality of the estimates. The fit of the three models was judged from comparison of the fraction of total variance in the PbB values explained (R^2 %). In addition plots of residuals versus time were used for checks of the validity of the models and the accuracy of the individual curve fittings.

To describe accumulation, a function of the form $Y(t) = A[1 - \exp(-B \times t)]$, where A is a scale constant, B an elimination constant, and t time, was fitted to the data by use of the nonlinear regression program in BMDP (21).

...e lead levels

...e lead levels were determined in vivo from the ...ge phalanx of the left forefinger of 37 subjects by ...-ray fluorescence method, as described earlier (16). ... detection limit was 20 μg/g, and the method er... about 15 %. Readings below the detection limit ... assigned a value of 10 μg/g in the calculations. ...most cases, levels derived either at duplicate ...surements (16) or calculated from a series of ...surements (15) were employed.

...atistics

...general, nonparametric tests were employed. For ...ations the Spearman's rank correlation (r_S) was ...ed, and for comparisons of duplicate measurements ...the same individual the Wilcoxon's matched-pairs ...ked-sign test was used. Comparisons between groups ...re made by the Mann-Whitney U-test. In a few in...nces, a single or multiple linear regression analysis ...s made. For establishing interindividual variations, ...omial tests were employed. When more than one ...ervation series was available for a particular in...vidual, the value corresponding to the calculations ...the best fit (R^2) of the compartment analysis was ...ed. All P-values are two-tailed. "Statistically sig...ficant" denotes $P < 0.05$.

...esults

...decline rate of PbB was, in most cases, rapid soon ...r end of exposure, but later on it was slower (figure ... There was generally a good fit of the observed PbB ...any of the three compartment models tested (tables ...nd 2). However, one subject (number 122) (table ...splayed pronounced irregularities in the elimina...n pattern, which rendered serious suspicion of oc...asional, ongoing exposure. In addition the lack of ...B data during the first 94 d after the stated end of ...posure probably contributed to the bad fit to any ...the models tested. He has thus been disregarded in ...e following results. Another ex-lead worker (number ...) was excluded because of suspected lead exposure ...ing the first month of the supposedly exposure-free ...iod (rising PbB). Furthermore, before the second ...servation period (from year 7 on), his PbB had ...creased to very close to the background level, and ...e $T\frac{1}{2}(2)$ was determined merely from the observa...ns made during the first year. No conclusions as ...ards the kinetics of a slow compartment seem to ...e justified in this case.

...or most of the ex-lead workers, the number of ob...rvations during the first period after the end of ex...sure was too few (less than four per two months) ...allow reasonably accurate estimates of the decay rate ...the fast compartment. Thus, for all but three (num...rs 102, 103, and 123), an approximate half-time of ...e fast compartment [$T\frac{1}{2}(1)$] of 30 d was employed. ...e the following text.)

The fit of the two-compartment model (median 97 %, range 35—99 %) was considerably and significantly ($P < 0.0001$, Wilcoxon) better than that of the one-compartment model (median 86 %) (tables 1 and 2). The fit of the three-compartment model was similar (medians 97 versus 97 %) (table 1), though significantly ($P < 0.01$, Wilcoxon) better.

When the three-compartment model was employed, the median of Y(1) was 0.6 (range 0.0—2.3) μmol/l, that of Y(2) was 1.4 (range 0.0—2.5) μmol/l, that of $T\frac{1}{2}(2)$ was 3.7 (range 0.3—16) years, that of Y (3) was 0.3 (range 0.0—2.6) μmol/l, and that of $T\frac{1}{2}(3)$ was >100 (range 4.9—00) years.

In the following presentation, only the simplest model with a good fit, ie, the two-compartment one, will be discussed.

With the use of the two-compartment model, the decay rate in the remaining 21 ex-lead workers (table 1) had a median biological half-time of the slow compartment [$T\frac{1}{2}(2)$] of 5.6 years during a median post-exposure period of 13 years. There was a considerable range for $T\frac{1}{2}(2)$, ie, 2.3—27 years (table 1).

The data were sufficient for an estimate of the half-time of the fast compartment in three of the ex-lead

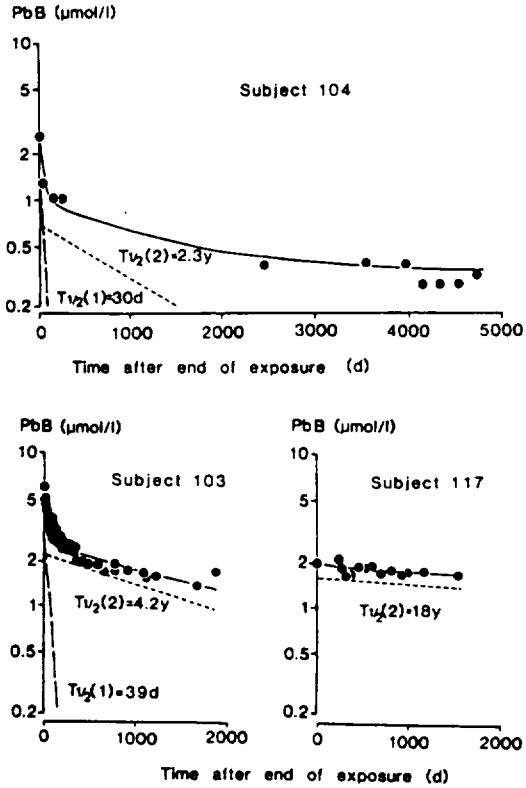


Figure 1. Decline of the blood lead level (PbB, logarithmic) after the end of exposure for three ex-lead workers. A two-compartment model was fitted to the data. Both compartments and their biological half-times ($T\frac{1}{2}$) are indicated. For subjects 104 and 117, the half-time of the fast compartment [$T\frac{1}{2}(1)$] was assumed to be 30 d. (y = years)

Table 1. Kinetics of the decrease of lead in blood (PbB) after the end of the occupational exposure of 23 ex-lead workers observed for more than one year. (R^2 = degree of explanation, T½(1) = half-time of fast compartment, T½(2) = half-time of slow compartment, 95 % CI = 95 % confidence interval, Y(1) = Y intercept for the fast compartment, and Y(2) = Y intercept for the slow compartment)

Subject[a]	Age[b] (years)	Exposure time (years)	First PbB (μmol/l)	Observation time (years)	Number of samples	One compartment model	Two-compartment model						
							Fast compartment			Slow compartment			
						R^2 (%)	T½(1) (d)	95 % CI	Y(1) (μmol/l)	T½(2) (years)	95 % CI	Y(2) (μmol/l)	R^2 (%)
101[c]	44	4.5	1.8	2.9	5	68	30[d]		0.0	3.7	2.0—27	1.9	68
102	60	5	4.2	15.0	39	87	29	21—47	1.4	8.4	7.6—9.5	2.6	97
103	49	10	5.9	5.1	40	68	39	33—47	3.0	4.2	3.4—5.7	2.2	98
104	54	35	2.7	13.0	11	87	30[d]		1.4	2.3	0.9—∞	0.7	95
105	41	3	3.0	12.9	10	88	30[d]		0.8	5.6	4.3—8.2	1.9	94
106	48	8	2.9	12.9	12	91	30[d]		1.0	4.6	4.2—5.1	1.6	99
107	54	34	3.3	13.0	13	94	30[d]		1.1	3.5	2.8—4.7	2.0	98
108	30	7	3.7	12.9	12	91	30[d]		1.2	4.6	4.2—5.2	2.2	99
109	59	27	2.6	12.9	12	79	30[d]		1.0	5.1	4.5—5.8	1.2	99
110	56	26	3.8	12.9	12	51	30[d]		1.7	7.6	6.7—8.8	1.8	99
111	65	45	3.3	12.8	12	86	30[d]		1.0	9.4	7.9—11.5	2.0	97
112	51	33	3.2	12.8	10	95	30[d]		0.5	5.8	5.0—6.9	2.3	98
113	66	44	3.0	11.2	9	96	30[d]		0.5	5.6	4.7—6.8	2.3	98
114	31	4	2.4	10.4	8	98	30[d]		0.2	0.8	0.5—2.5	2.0	98
115	63	45	2.2	9.4	6	96	30[d]		0.3	3.9	3.3—4.8	1.6	99
116	67	10	4.3	13.2	9	82	30[d]		1.4	8.7	6.7—12.4	2.5	97
117[c]	59	27	2.0	4.2	14	31	30[d]		0.1	18	8.1—0.0	1.6	35
118	58	22	1.9	4.9	10	78	30[d]		0.4	6.5	4.3—13.8	1.2	91
119	65	30	2.8	4.6	13	86	30[d]		0.8	4.7	4.0—5.8	1.8	98
120	65	33	2.3	4.6	14	64	30[d]		0.6	9.5	6.2—21.3	1.3	89
121	65	14	1.8	4.3	17	78	30[d]		0.4	4.3	3.3—6.4	1.0	92
122	61	24	1.8[e]	3.6	12	9	30[d]		4.8	0.0	∞—∞	1.4	0
123	65	38	2.0	1.7	12	27	7	2—∞	0.3	27	5.5—∞	1.5	50

[a] Number 101 was a cast bronze founder, number 102 a spray painter, numbers 103—115 storage battery workers, number 116 a wire lead [illegible] and numbers 117—123 smeltery workers.
[b] At the end of exposure.
[c] Numbers 101 and 117 are identical with numbers 201 and 217, respectively, in table 2.
[d] When fewer than four samples were obtained during the first two months after the end of exposure, the T½(1) was assumed to be 30 d.
[e] Sample obtained 94 d after the end of exposure.

Table 2. Kinetics of the decrease of the blood lead (PbB) levels during a temporary cessation of occupational exposure among 17 lead [illegible] observed for less than one year and among two volunteers who had a short, heavy exposure. (R^2 = degree of explanation, T½(1) = half-time [illegible] fast compartment, T½(2) = half-time of the slow compartment, 95 % CI = 95 % confidence interval, Y(1) = Y intercept for the fast compartment, T[illegible] intercept for the slow compartment)

Subject[a]	Age[b] (years)	Exposure time (years)	First PbB (μmol/l)	Observation time (d)	Number of samples	One compartment model	Two-compartment model				
							Fast compartment			Slow compartment[c]	
						R^2 (%)	T½(1) (d)	95 % CI	Y(1) (μmol/l)	Y(2) (μmol/l)	
201[d]	43	3	6.7	189	20	87	26	21—35	3.6	2.6	
202	59	23	4.5	209	12	87	43	25—147	1.2	2.7	
203[e]	59	22	4.2	172	10	94	69	38—337	2.1	1.9	
	60	23	5.4	118	14	96	49	36—75	2.8	2.3	
204	53	22	4.0	239	12	88	37	25—74	1.3	2.2	
205	38	14	3.9	48	7	89	14	7—∞	1.2	2.2	
206	60	5.5	3.0	112	11	92	28	18—61	1.1	1.5	
207	52	29	3.0	218	12	73	63	20—∞	0.5	2.0	
208[e]	28	3.5	3.4	114	10	94	34	24—55	1.5	1.7	
	29	4.0	3.2	115	11	94	24	18—36	1.2	1.6	
209	48	7.5	3.5	171	11	78	13	8—38	1.3	1.8	
210	58	3.5	3.9	160	11	92	47	28—139	1.5	1.8	
211	59	13	2.8	155	12	54	8	5—18	0.6	1.9	
212	49	10	3.5	238	13	59	7	5—10	0.8	2.4	
213	51	1.5	3.0[f]	120	10	87	20	14—34	1.9	1.6	
214	40	1.0	3.5	155	12	97	50	38—75	2.0	1.0	
215	50	1.0	3.3	147	9	84	24	19—35	1.4	1.7	
216	29	0.3	3.5	83	11	97	42	24—171	2.4	0.9	
217[d]	59	26	3.0	111	9	96	63	31—∞	1.5	1.2	
318	33	0.0001	2.1	215	12	94	27	17—62	1.4	0.1	
319	37	0.0001	2.3	500	13	97	44	32—71	1.7	0.1	

[a] Number 201 was a cast bronze founder, numbers 202—205 demolition workers, numbers 206—217 smeltery workers, and numbers 318—[illegible] unteers.
[b] At the end of exposure.
[c] T½(2) is assumed to be 5 years.
[d] Numbers 201 and 217 are identical to numbers 101 and 117, respectively, in table 1.
[e] Two subjects were studied twice. In the statistical calculations, the decay pattern with the best fit was used.
[f] Sample obtained 15 d after the end of exposure.

...(numbers 102, 103, and 123) (table 1) and in ...porarily removed lead workers (table 2). The ...ion period in the latter group was too short ... accurate estimation of the half-time of the slow ...ment [T½(2)]. Thus, in the calculation of ... for these subjects, an approximate T½(2) of ... (see the preceding text) was used as being the ...imate. The median T½(1) for the 20 subjects ... d. Their median observation time was 155 d. ... of T½(1) was considerable (7—63 d) (table ... subjects 203 and 208, the T½(1) with the best ... d and 24 d, respectively, being used. The decay ... with the shortest and next longest T½(1), ...ively, are shown in figure 2.

...In two subjects (numbers 203 and 208) (ta... the decay pattern was studied during two pe... of temporary removal from exposure, 0.5 and ... years apart, the decline rates of PbB were com...ble.

...two formerly occupationally unexposed subjects ... T½(1) of 27 and 44 d (table 2).

...Y intercept of the fast compartment [Y(1)] had ...dian of 0.8 (range 0.0—3.0) μmol/l for the 21 ex... workers (table 1), and 1.3 (range 0.5—3.6) μmol/l ... 17 temporarily removed ones (table 2). The dif... was statistically significant (P = 0.007, Mann-...).

...Y intercept of the slow compartment [Y(2)] had ...dian of 1.8 (range 0.7—2.6) μmol/l for the 21 ex... workers (table 1) and a median of 1.8 (range 0.9— ... μmol/l for the 17 workers temporarily removed ... exposure (table 2). The groups were, of course, ... significantly different. For both of the two oc...ionally unexposed subjects, Y(2) was 0.1 μmol/l. ... the 21 ex-lead workers, Y(2) made up for a ...dian of 68 (range 33—100) % of the combined com...ents [Y(1) plus Y(2)], whereas for the workers

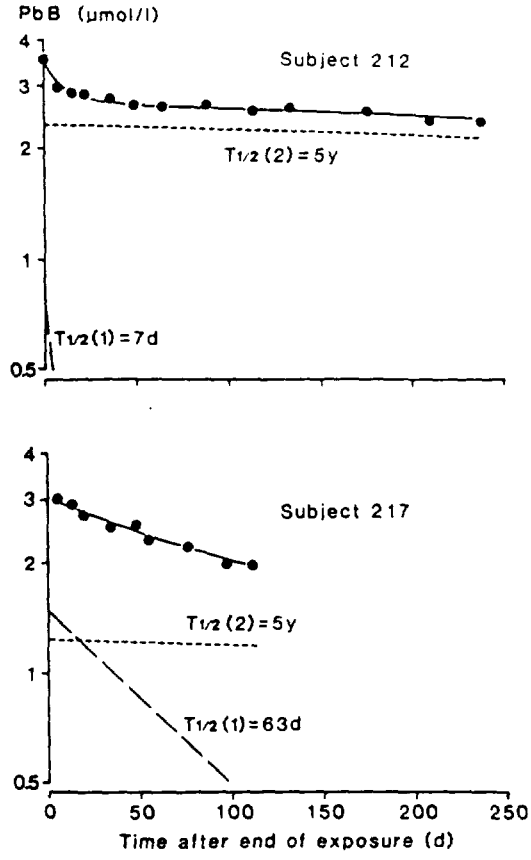
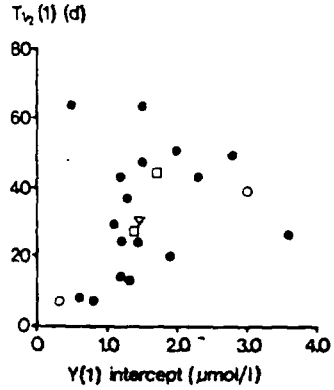


Figure 2. Decline of the blood lead level (PbB, logarithmic) in two lead workers temporarily removed from exposure. A two-compartment model with a biological half-time (T½) of 5 years for the slow compartment was fitted to the data. Both compartments and their half-times are indicated (From subject 217, the first blood sample was taken 6 d after the end of exposure.) (y = years)



...gure 3. Relationship between the half-time (T½(1)] and the ...ntercept [Y(1)] of the fast compartment in a two-...partment model fitted to the decline of the blood lead ...el levels after the end of exposure. Closed circles and open ...cles denote lead workers and volunteers, respectively, in ...re 2, open circles and triangles denote ex-lead workers in ...re 1. (Circles = subjects studied up to 5 years, triangles = ...bjects studied more than 5 years)

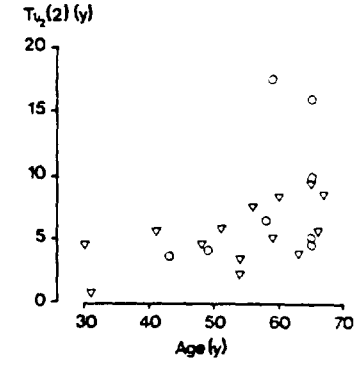


Figure 4. Relationship between age and the half-time of the slow compartment (T½(2)] in a two-compartment model fitted to the decline of blood lead levels after the end of exposure. Symbols as in figure 3. (y = years)

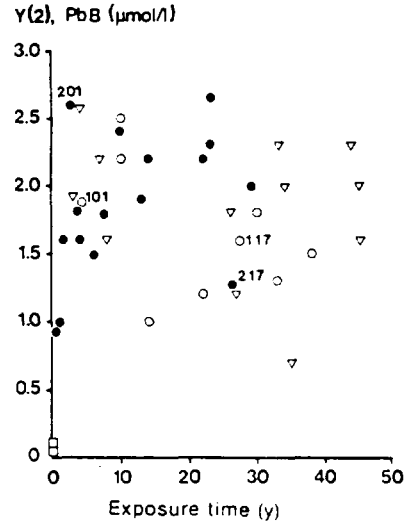


Figure 5. Relationship between time of occupational lead exposure and Y intercept of the slow compartment [Y(2)] in a two compartment model fitted to the decline of the blood lead (PbB) levels after the end of exposure. Symbols as in figure 3. Subjects 101 and 117 are identical with 201 and 217, respectively. (y = years)

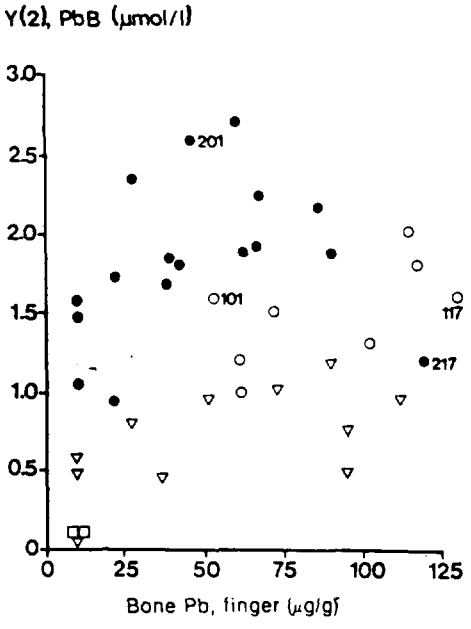


Figure 6. Relationship between the lead level in finger bone (Bone Pb) and the Y intercept of the slow compartment [Y(2)] in a two-compartment model fitted to the decline of blood lead (PbB) after the end of exposure. Symbols as in figure 3. Subjects 101 and 117 are identical with 201 and 217, respectively. Note: The "Y(2)" values are not the same as in tables 1 and 2, as they have been recalculated to the time of the first bone lead determination. The symbols in the shaded area represent bone lead levels below the detection limit (20 μg/g).

temporarily removed from exposure it was 57 (range 27—80) %. The difference was statistically significant ($P = 0.02$, Mann-Whitney). For all the lead workers the median was 65 %, while the fractions were 6 and 7 % for the two occupationally unexposed subjects.

$T½(1)$ correlated significantly with Y(1) ($r_s = 0.4$, $P = 0.03$) (figure 3), but not with age, time of exposure, initial PbB, Y(2), or the serum creatinine levels. For five out of the 20 subjects with an individually estimated $T½(1)$, the linear regression line for $T½(1)$ upon Y(1) [$T½(1) = 5.4 \times Y(1) + 23$] did not run through the 95 % confidence interval of $T½(1)$. This result showed that there was a statistically significant ($P = 0.03$, binomial test) interindividual variation for $T½(1)$.

The $T½(2)$ of the ex-lead workers correlated significantly with age ($r_s = 0.50$, $P = 0.01$) (figure 4), but not with exposure time, observation time, initial PbB, Y(1), Y(2), or the serum creatinine levels. In 10 out of the 21 subjects, the linear regression line for $T½(2)$ upon age [$T½(2) = 0.15 \times \text{age} - 1.7$] did not run through the confidence interval of $T½(2)$. This finding showed that there was an interindividual variation for $T½(2)$ ($P < 0.0001$).

When Y(2), for all 38 lead workers and the two unexposed subjects, was plotted against exposure time (figure 5), there was no significant nonparametric association. Neither was there any linear correlation. However, when an exponential accumulation curve was fitted to the data, there was a reasonable fit ($R^2 = 49$ %, $P < 0.001$). The elimination constant was 1.2, corresponding to a half-time of 0.6 years, and Y(2) leveled off at 1.8 μmol/l.

Moreover, there was a tendency for the workers temporarily removed from exposure to have a higher Y(2) at a particular exposure time than the ex-lead workers. However, the difference was not statistically significant in the multiple regression analysis. Neither did the observation time display any significant association with Y(2).

For the 35 lead workers and the two unexposed subjects, there was a significant correlation between Y(2) and bone lead content ($r_s = 0.36$, $P = 0.01$) (figure 6). Multiple linear regression analysis displayed that there was an increase in Y(2) of 0.008 μmol/l per μg/g bone-Pb ($P = 0.005$). Furthermore, the temporarily removed workers had a Y(2) that, on the average, was 1.0 μmol/l higher than that of the ex-lead workers. This finding was also obvious from the decrease in Y(2) of 0.09 μmol/l per year of the postexposure observation time ($P < 0.0001$). Among the active workers, there seemed to be a leveling off of Y(2) when the bone lead content increased. There was no such clear corresponding tendency among the retired workers.

Discussion

A multiple exponential model fitted well the decay pattern of PbB. However, there are other possibilities, e.g. power functions. Indeed, data indicating a nonlinear

...tion between the air lead level and PbB (eg, in references 12, 13, 19), between PbB and plasma lead (20, ... 45), and between PbB and the lead level in urine ... 13, 56, 67) could favor the choice of a nonlinear ...del. However, elimination rates similar to ours have ...en reported earlier, both for subjects far less (11, ... 53) and far more (14, 46) exposed. In addition there ... no indication in the present data that the elimina... rates were faster in subjects with a high initial PbB; ...ead the T½(1) increased with increasing Y(1). Thus ...re are at present no serious objections against the ... of a multiple exponential model, at least not in the ...B concentration range that we have studied.

For a few subjects, the fit was not as good. For five ...cts the R^2 was < 80 %, and for one of them it ... 0 %. This result may be due to the fact that, in ... subjects, the PbB was low during a major part ... the observation period and that thus the analytical ... had a great impact.

...s relevant to consider whether the number of com...ents is two. Different authors have proposed one ... (8), two (1, 7, 63, 64), three (4, 33, 43, 53, 66), ... (13, 23, 44, 45, 60), and even five (6) compart...ents in human metabolic models. The simplest mod... gave a good fit in the present study was the two-...partment one. Thus there was no reason to choose ...re complicated model. Of course, from a theo...al point of view, a larger number of compartments ...sable. Thus data from the two subjects exposed ... to a single heavy lead dose may indicate an initial ...ast decay of PbB (56). For most of the subjects ... present study, such a phenomenon would have ...ained undetected. There was probably a continuous ...ption of lead from the lungs and gastrointestinal ... for some time after the end of exposure. (See the ...owing discussion.) In addition the early observa... were few. However, for the two subjects (num... 208 and 216) from whom frequent observations ... made during the first few days after the end of ...sure, the data did not indicate any rapid initial ...ase. Moreover, in addition to the relatively small ...er of observations, the limited observation period ... the analytical method error may obscure other ...partments, especially small or very slow ones. In... some observations in the present study may in...ate that the slow compartment really has more than ...component. (See the following discussion.)

...e parts of the body which constitute the two com...ents must also be considered. The only organ ...aining lead amounts sufficiently large to cover the ...derable excretion associated with the decay of the ...compartment [on the order of 0.05—0.1 mg/24 h ...e only, for several years (60)] is the skeleton, ...contains hundreds of milligrams (1, 15, 16, 39, ...). The identity between the slow compartment and ...etal pool is also strongly supported by the as...tion between Y(2) and the bone lead content. The ...issues, including the lung, contain only a few mil... (10, 59), an amount which fits with the excretion during the emptying of the fast compartment.

The median half-time of the fast compartment was about one month. There may be errors that affect this estimate. It is difficult to be absolutely sure that the exposure did stop totally at a fixed date; some exposure may have continued after the formal end of exposure. For example, for the temporarily removed smeltery workers, the worksite after removal was located only a few hundred meters from the plant. Also, the homes of the workers may have been contaminated. In addition, a worker may have a pool of lead in the lungs and the gastrointestinal tract and thus continue to absorb lead for some time after lead inhalation and ingestion have ceased. The limited data on hand — frequent measurements of two subjects — may indicate such an absorption, but mainly up to one week after the end of exposure, which is in accordance with earlier observations (9, 12, 13, 31, 32). This delayed absorption is probably the reason of the present weak positive correlation between T½(1) and Y(1). These possible sources of error all tend to give a somewhat too long an estimate as compared to the true half-time. Furthermore, the workers temporarily removed from exposure were not randomly selected. They were removed from exposure because of high PbB levels, and this occurrence might partly be the result of a slow elimination rate in those particular individuals. Another possible explanation of the slight positive association between T½(1) and Y(1) is a bias introduced by the disregarding of possible intermediate compartments.

PbB is mainly present in the red cells. It could thus be suspected that the lifetime of these cells would determine the T½(1). However, the calculated T½(1) is considerably shorter than would be expected if lead were eliminated from blood only at the normal death of these cells. But lead is known to cause hemolysis, and the question can be raised of whether it could have affected the T½(1). Hardly, at least not considerably, as there was no correlation between T½(1) and the initial PbB. A negative correlation would be expected if hemolysis were important. For the lead workers temporarily removed from exposure, we had to employ an estimated T½(2) of five years. However, this procedure did not affect the T½(1); even a T½(2) as short as one year, or as long as 10 years, would cause only slight changes in the T½(1).

Having taken these possible errors into consideration, we still find it fully justified to conclude that the average T½(1) is about one month. This assumption is also compatible with various kinds of earlier data on the elimination (1, 11—14, 20, 27—29, 36, 37, 40, 46, 50, 53, 54, 56, 65), if a second, slow compartment is taken into consideration, and on the accumulation (5, 24, 27, 28, 37, 38, 48, 65, 67) of PbB.

There was a considerable interindividual variation in T½(1). To some degree this occurrence may be explained by various errors in the estimates of individual decay curves. Thus the two subjects studied twice had

trabecular (or cancellous) bone pool may be more important (57). But, in addition, in the active workers, Y(2) may also be affected by a small, intermediately exchangeable pool, perhaps contained mainly in the liver, the kidneys (10, 59), and the skeleton (an even faster pool than the trabecular one). When the data of subject 103 in figure 1 is closely examined, one may, in fact, anticipate more than one component in the slow compartment.

The impact of organs other than the skeleton on Y(2) may be indicated by the accumulation pattern of Y(2) with increasing exposure time. A steady state was reached already within a couple of years. This period is faster than in trabecular bone (57); the turnover of cortical bone is much slower (15, 61). The accumulation pattern may also be affected by the nonlinear behavior of lead in erythrocytes (19, 40, 43). This phenomenon may also be the cause of the apparent leveling off of Y(2) upon lead in finger bone in active workers (but not in the retired ones, who had lower PbB levels).

There was a considerable interindividual variation in Y(2) at a particular exposure time. One obvious explanation is variations in the intensity of exposure. An additional explanation may be the interindividual variations in lead metabolism seen in this study, as well as in earlier ones (8, 32, 60).

The variation in the kinetics of lead metabolism would mean a considerably varying risk for different individuals exposed at the same level, which, of course, is important from a practical point of view. A short T½(1), as the result of a rapid excretion, is probably an advantage for the worker. On the contrary, a long T½(2) may be good, as it means that the net endogenous exposure from the skeleton is low.

In many countries, lead workers are removed from lead exposure when they reach a PbB "trigger level" or "removal level"; in Sweden at present 3.0 μmol/l), and they are not allowed to return until the PbB concentration has decreased to a "safe level" ("return level"; 2.0 μmol/l). In our "typical" lead worker, who had an Y(2) of 1.8 μmol/l and a T½(1) of one month, this process will take as much as about six months. However, newly employed workers, who have a small Y(2), would display the same decay in less than a month. On the other hand, as many as 57 % (24 of 42) of our workers had a Y(2) of more than 1.7 μmol/l. With the assumption of a "background" level of 0.3 μmol/l, they would reach 2.0 μmol/l only after a sufficiently long time had elapsed to affect the slow component. In the workers who were followed for a long time, 30 % (7 of 23) would require more than a year to reach the "safe level." These assumptions are in accordance with observations of workers removed from exposure (49).

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